wherein:

n is an integer from 2-8;

X_1 is a cholic acid group or deoxycholic acid group; and X_2 and X_3 are each independently selected from the group consisting of a cholic acid group, a deoxycholic acid group, and a saccharide group, wherein the saccharide group is selected from the group consisting of pentose monosaccharide groups, hexose monosaccharide groups, pentose-pentose disaccharide groups, hexose-hexose disaccharide groups, pentose-hexose disaccharide groups, and hexose-pentose disaccharide groups;

and wherein at least one of X_2 and X_3 is a saccharide group.

60. The composition of claim 59, wherein the diagnostic agent is a marker gene.

61. (New) The composition of claim 60, wherein the marker gene encodes a polypeptide selected from the group consisting of β-galactosidase, green fluorescent protein, and luciferase.

REMARKS

The Claimed Invention

This invention provides compounds that enhance the delivery of a therapeutic or diagnostic agent to a cell or tissue. Methods for administering a therapeutic or diagnostic agent to a cell using the compounds, and compositions that contain the delivery-enhancing compounds, are also provided, as are methods for treating bladder cancer. Included among the therapeutic and diagnostic agents that can be delivered are proteins and nucleic acids, including gene therapy vectors.

Status of the Application

Claims 1-61 are pending with entry of this amendment, with claims 1-55 previously pending and claims 56-61 added by way of this amendment.

Claims 1-55 stand rejected under 35 USC § 112, first paragraph. Claims 1, 7, 12, 16, 23, 29, 41-42 and 45 stand rejected under 35 USC § 102(b). Claims 1-6, 8, 12-15, 17, 23-26, 30 and 39-40 stand rejected under 35 USC § 103(a), and claims 1, 8-9, 11-12, 17-18, 20, 23, 30-31, 33 and 37 stand rejected under 35 USC § 103(a) on a different ground. Claims 21-22, 35-36, 43-45 and 46-51 are indicated as being free of the art.

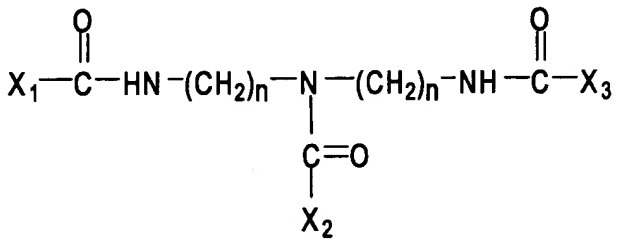
The Amendments

The entry of the requested amendments does not add new matter to the application. New claims 56-61 find support in the application at, for example, page 10 lines 7-16 ("The delivery-enhancing agents of the invention can be used to formulate therapeutic or diagnostic agents . . . . . Examples of diagnostic agents include marker genes (such as but not limited to β-galactosidase, green fluorescent protein, and luciferase) . . . ."). Support is also found in originally filed claims 1 and 12.

The 35 U.S.C. § 112, First Paragraph Rejection

Claims 1-55 stand rejected under 35 USC § 112, first paragraph, because the claims allegedly include subject matter that is not described in the specification in such a way as to enable one of skill in the art to make and/or use the invention. Applicants respectfully traverse this rejection.

A first ground of this rejection is apparently based on a misunderstanding of Applicants' invention, namely, an assumption that Big CHAP falls within the scope of the formula recited in Applicants' claims. However, Big CHAP is not among the compounds encompassed by the formula set forth in Applicants' independent claims 1, 12, 23, and 41, which is as follows:



The claims specify that, in relevant part, X_1 is a cholic acid group or a deoxycholic acid group, while X_2 and X_3 are each independently selected from the group consisting of a cholic acid group, a deoxycholic acid group, and a saccharide group.

This formula does not encompass Big CHAP, as evidenced by the formula for Big CHAP as shown on page 230 of the Aungst *et al.* reference. X_1 and X_2 are both saccharide groups (glucose) in Big CHAP, while the cholic aid group of Big CHAP is attached to the position shown as X_2 in Applicants' formula. Given that Applicants' formula requires that X_1 be a cholic acid or a deoxycholic acid group, while Big CHAP does not have either of these groups at the X_1 position, Big CHAP is not a species within the scope of Applicants' claims. Thus, Applicants' claims are not directed to methods of enhancing delivery of a therapeutic agent to a cell by formulating the agent in a composition that comprises Big CHAP.

The rejection cites experiments described in Applicants' specification which demonstrate that not all Big CHAP preparations confer an enhancing effect on delivery of therapeutic agents, and that it is impurities in Big CHAP preparations that are the active ingredients that are responsible for the observed enhancement. The rejection then states that "[o]ne of skill in the art would not know what impurities are essential for BigCHAP to obtain an increase in gene expression either for a therapeutic or marker use. The specification fails to provide adequate guidance to obtain an increase in gene expression using **any** BigCHAP of **any** lot with **any** impurities" (page 3, emphasis in original). It is, however, the impurities themselves that are encompassed by the formula set forth in Applicants' claims, not Big CHAP. It is these impurities that are the active ingredients found in some commercial preparations of Big CHAP that are responsible for the observed enhancement of delivery of therapeutic agents, as demonstrated in Example 11 of Applicants' specification. Example 12 describes how one can

synthesize a representative example of the compounds encompassed by the formula in Applicants' claims, and given this teaching, the synthesis of other such compounds is a routine matter for those of ordinary skill in the art. Therefore, Applicants' specification provides a disclosure that is fully enabling for the claimed invention.

The rejection asserts that "[e]xamples 8 . . . and 6 . . . demonstrate the expression of p53 and retinoblastoma (RB) genes, respectively, using BigCHAP, but do not determine the level of expression. . . . There is no evidence of the enhanced expression of a therapeutic gene as disclosed in the specification" (page 4, first paragraph). Contrary to this statement, Applicants' specification does demonstrate enhanced expression of a therapeutic gene. For example, as stated in Example 6 (page 25), the administering an RB-expressing adenoviral vector resulted in "enhanced expression using an ethanol of Big CHAP (CALBIOCHEM®) formulation," for which results "are shown in Figure 9." Similarly, Example 8 (page 27) showed expression of p53 in bladder tumors when an adenoviral vector was administered in a Big CHAP-containing formulation. Moreover, Applicants' specification contains several examples demonstrating that expression of a marker gene (β-gal) is enhanced when administered using formulation that contains the compounds encompassed by Applicants' claims.

The rejection asserts that the gene therapy art was unpredictable at the time Applicants' invention was made. In support of this rejection, four references are cited. However, Applicants respectfully submit that these references, taken alone, do not provide a true understanding of the state of the art of gene therapy, and in particular of the use of gene therapy to treat cancer. A much more accurate picture of the state of the art of gene therapy is provided by the number of gene therapy clinical trials that are currently underway, including Phase II and Phase III trials. As of December 1, 1998, 366 gene therapy trials have been published or are underway, of which 230 are directed to cancer gene therapy (Wiley Clinical Trials Database, http://www.wiley.com/genetherapy/diseases.html). Of the 367 gene therapy clinical trials, 32 are in Phase II, and 2 are in Phase III. Fifty-nine of the trials used adenoviral vectors. Importantly, at least 20 of these gene therapy clinical trials had commenced prior to Applicants' priority date. *Id.*

Just obtaining FDA approval to conduct clinical trials in humans requires a demonstration of pharmaceutical efficacy that is more than sufficient to satisfy the requirements

for patentability under 35 USC § 112 and 101. As stated in the MPEP, "[b]efore a drug can enter human clinical trials, the sponsor, often the applicant, must provide a convincing rationale to those especially skilled in the art (e.g., the Food and Drug Administration) that the investigation may be successful. . . . Thus, as a general rule, if an applicant has initiated clinical trials for a therapeutic product or process, Office personnel should presume that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility" (MPEP § 2107.02, emphasis in original). In the face of the avalanche of clinical trials that have been approved by the FDA, no basis exists for the Office Action's position that the state of the art for gene therapy in general is so unpredictable as to render any gene therapy-related inventions *per se* unpatentable.

Moreover, Applicants note that some of the references cited in support of the rejection indicate that the success of gene therapy would be facilitated by improvements in the ability to deliver genes to cells. Ironically, it is compounds and methods for increasing gene delivery that are provided by Applicants' invention. Applicants' specification provides experimental results which demonstrate that the use of the claimed compositions to deliver genes does result in a marked increase in gene delivery and expression. Therefore, Applicants' invention provides a significant step towards solving a problem that has been identified as being of concern in gene therapy.

Claims 7, 16 and 29 are directed to methods of administering a protein, and compositions that contain proteins, in which the specified delivery enhancing agents are employed. Applicants respectfully submit that the description of these claims in the rejection, and thus the rejection itself, is unclear. The rejection states that the claims are "towards methods of treating disease, specifically bladder cancer, by administering a protein formulated in a buffer comprising a compound claimed without causing **any** phenotypic change to the host." However, only one of these three claims specifies treating bladder cancer, or any other disease. Claim 7 is directed to a method of administering a protein to a cell, claim 16 is directed to a pharmaceutical composition that comprises a protein. Moreover, it is unclear what is meant by the phrase "without causing any phenotypic change to the host." The PTO has the initial burden of making a *prima facie* case of showing that a claimed invention is not enabled under 35 USC § 112, first

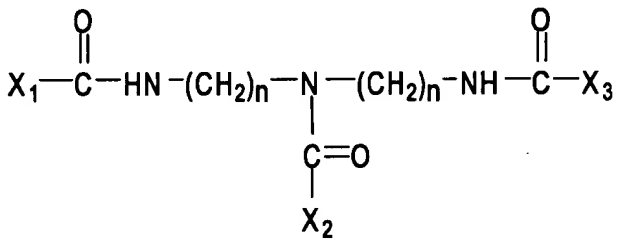
paragraph (MPEP § 2164.04). As this ground of rejection is not supported by any specific evidence or reasoning, the *prima facie* case of non-enablement is not established. Accordingly, this rejection should be withdrawn.

Applicants note that this rejection, as it relates to a therapeutic effect, is not applicable to newly added claims 56-61.

The 35 U.S.C. § 102(b) Rejection

Claims 1, 7, 12, 16, 23, 29, 41-42, and 45 stand rejected under 35 USC § 102(b) as allegedly being anticipated by Aungst *et al.* (*Int. J. Pharm.* (1993) 53: 227-235). Applicants respectfully traverse.

As the Examiner correctly notes, the cited reference discusses delivery of insulin in a formulation that includes Big CHAP. Big CHAP, however, is not within the scope of the formula set forth in each of Applicant's claims. As discussed above, the formula set forth in Applicants' independent claims 1, 12, 23, and 41 is as follows:



The claims specify that, in relevant part, X_1 is a cholic acid group or a deoxycholic acid group, while X_2 and X_3 are each independently selected from the group consisting of a cholic acid group, a deoxycholic acid group, and a saccharide group.

This formula does not encompass Big CHAP, as evidenced by the formula for Big CHAP as shown on page 230 of the Aungst *et al.* reference. X_1 and X_2 are both saccharide groups (glucose) in Big CHAP, while the cholic aid group of Big CHAP is attached to the position shown as X_2 in Applicants' formula. Given that Applicants' formula requires that X_1 be a cholic acid or a deoxycholic acid group, while Big CHAP does not have either of these groups at the X_1 position, Big CHAP is not a species within the scope of Applicants' claims. Therefore, because

the Aungst *et al.* reference does not describe each element set forth in Applicant's claims, the reference does not anticipate Applicants' claimed invention.

The 35 U.S.C. § 103 Rejection

Claims 1-6, 8, 12-15, 17, 23-26, 30 and 39-40 stand rejected under 35 USC § 103(a) as allegedly being unpatentable over Aungst *et al.* (*Int. J. Pharm.* (1993) 53: 227-235) in view of Carson *et al.* (US Patent No. 5,804,566, issued September 8, 1998 and filed November 1, 1994). Applicants respectfully traverse this rejection.

A proper *prima facie* case of obviousness requires that all of the claim limitations must be taught or suggested by the prior art. MPEP § 2143.03, *citing In re Royko*, 180 USPQ 580 (CCPA 1974). This requirement is not satisfied by the instant rejection.

As discussed above with respect to the 35 USC § 102(b) rejection, the Aungst *et al.* paper does not describe a compound that is within the scope of the formula set forth in Applicants' claims. According to Applicants' claims, X_1 in the formula must be a cholic acid or a deoxycholic acid group, while Big CHAP does not have either of these groups at the X_1 position. The Carson *et al.* reference likewise fails to set forth a compound within the scope of the formula in Applicants' claims. Nor does either reference, alone or in combination, suggest the inclusion of the compounds in a pharmaceutical composition, or the use of such compounds to administer a therapeutic agent (*e.g.*, a gene) to a cell, or to treat bladder cancer. In the absence of this suggestion, *prima facie* obviousness is not established so this ground of rejection should be withdrawn.

Claims 1, 8-9, 11-12, 17-18, 20, 23, 30-31, 33 and 37 stand rejected under 35 USC § 103(a) as allegedly being unpatentable over Aungst *et al.* in view of Carson *et al.*, and further in view of Takahashi *et al.* (*Proc. Nat'l. Acad. Sci. USA* (1991) 88: 5257-5261). As does the previous ground of rejection, this rejection relies upon the Aungst *et al.* paper to provide the suggestion to use a specific compound that is within the scope of the formula set forth in Applicants' claims. However, as pointed out above, Big CHAP is not a species that is encompassed by this formula. Nor does either of the secondary references describe the use of a compound such as are set forth in Applicants' claims. Therefore, because the cited references fail

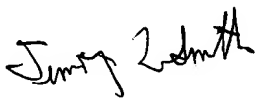
to teach or suggest each element of Applicants' claims, this ground of rejection is improper and should be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe that all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned attorney at (415) 576-0200.

Respectfully submitted,



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